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PHENOL ETHERS CONTAINING BASIC GROUPS AND METHOD OF PREPARING THESE COMPOUNDS

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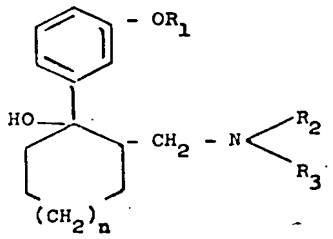
The present invention relates to new and valuable compounds of the following general formula



I

wherein R_1 represents an alkyl radical containing 1 - 3 carbon atoms or an aralkyl radical, R_2 and R_3 have the same or a different meaning and represent alkyl radicals containing 1 - 6 carbon atoms or aralkyl radicals, or together with the nitrogen atom represent a morpholine or pyrrolidine group, and n represents zero, 1 or 2, and the esters of these compounds with hydrogen halides or lower alkanoic acids, as well as salts of these compounds with acids.

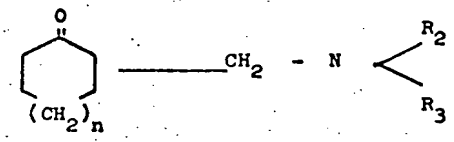
The compounds of the general formula I, especially those in which n stands for 1 and R_2 and R_3 represent methyl radicals, exhibit strong analgesic activity and are in most cases well tolerated. For example, the ED_{50} (this figure represents that amount of the compound after the application of which 50 % of the test animals do not react any more to pain) for the hydrochloride of 1-(m-methoxyphenyl)-2-dimethylaminomethyl-cyclohexanol-(1) (in the following referred to as compound A) when applied orally, is 23.5 mg/kg mouse body weight. The DL_{50} (this figure represents that amount of the compound after the application of which 50 % of the animals die) of compound A when applied orally, is 395.0 mg/kg mouse body weight. Moreover, compounds of formula I possess very good antitussive properties, e.g. when applied intravenously, 2.5 mg of compound A per kg cat body weight cause inhibition of 75 % of mechanically provoked cough reflex of a narcotized cat. This cough reflex is inhibited by intravenous application of 2.5 mg of the hydrochloride of 1-(m-methoxyphenyl)-2-pyrrolidinomethyl-cyclohexanol-(1) per kg cat body weight to a degree of 63 %, and of 1 mg of the hydrochloride of 1-(m-benzyloxyphenyl)-2-pyrrolidinomethyl-cyclohexanol-(1) per kg cat body weight to a degree of 65 % and of 2.5 mg of the hydrochloride of 1-(m-methoxyphenyl)-2-

N-methyl-N-(β-phenylethyl)-aminomethyl-cyclohexanol-(1) per kg cat body weight to a degree of 100 %, respectively. Compounds with a more or less similar structure, e. g. 1-(p-methoxyphenyl)-2-dimethylaminomethyl-cyclohexanol-(1) (compound B) or the 1-(m-methoxyphenyl)-2-piperidinomethyl-cyclohexanol-(1) (compound C) are known. However, the ED_{50} of these compounds, when applied orally, for testing the analgesic properties, amounts to more than 100 mg/kg mouse, which is especially unsatisfactory with respect to compound C, because after application of this compound in an amount of 200 mg/kg mouse, toxic reactions occur (two of ten animals died after being treated with this amount of compound C). After intravenous application of 2.5 mg/kg cat of compound B, mechanically provoked cough reflex of a narcotized cat is not influenced. The same amount of compound C causes an inhibition of only 38 % of the cough reflex.

The cyclohexane ring in the compounds of formula I contains two carbon atoms which each bear four different substitutents. This configuration causes a cis-trans-isomerism, the isomers being separatable into optically active forms by conventional methods. The cis-trans-isomers may be separated from each other for instance by distillation of the free bases, by recrystallization of salts or by other methods known per se.

The pharmacological data given above were obtained with mixture of the different forms of the compounds, the mixtures being obtained by the route of synthesis described in the following.

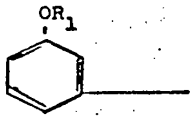
The compounds of formula I may be obtained by reacting a compound of the general formula



II

wherein R_2, R_3 and n have the meanings given above,

with a compound of the general formula



X III

wherein R_1 has the meaning given above and wherein X represents a lithium atom or the group MgHal, Hal representing a halogen atom,
in the presence of an ether which preferably is of the cyclic type, and hydrolyzing the intermediate thus obtained to give the compounds of formula I, which then may be transformed into salts with acids and/or into esters with lower alkanoic acids or hydrogen halides.

For esterification with lower alkanoic acids the compounds of formula I are preferably reacted with halides or anhydrides of these acids.

The reaction of the compounds of the general formula II with the compounds of the general formula III is preferably made at temperatures between -50 and +100°C. For hydrolysis of the intermediates the reaction mixture is treated, preferably while cooling, with water which may contain ammonium salts or with diluted acids.

The following examples serve as further illustration of the invention. All melting and boiling points are uncorrected.

Example 1

Five g of magnesium turnings are treated while stirring with a mixture of 37.4 g of m-bromoanisole and 160 ml of absolute tetrahydrofuran in such a rate that the reaction mixture boils gently on account of the heat produced by the immediately starting reaction. Thereafter, the reaction mixture is refluxed while being stirred until the magnesium is dissolved.

The reaction mixture is cooled to 0 to -10°C and then a mixture of 23.25 g of 2-dimethylaminomethyl-cyclohexanone and 45 ml of absolute tetrahydrofuran is added dropwise. The mixture is stirred for about 4 hours at room temperature and then poured, while stirring slowly into a mixture of 25 g of ammonium chloride, 50 ml of water and 50 g of ice. The layers are separated and the aqueous layer is extracted twice with portions of 50 ml of ether each. The organic layers are combined, dried with sodium sulfate and evaporated. The residue is distilled, whereby the 1-(m-methoxyphenyl)-2-dimethylaminomethyl-cyclohexanol-(1) is obtained in a yield of 78.6 % of the theoretical one. Boiling point: 138-140° C/0.6 mm Hg.

The hydrochloride obtained from the product e.g. by dissolving in

ether and treating with dry hydrogen chloride, melts at 168-175° C. By recrystallization from moist dioxane this hydrochloride is separated into isomers melting at 162-163° and 175-177° C respectively. On heating the mixture of the isomers with acetic anhydride, one obtains the hydrochloride of 1-(m-methoxyphenyl)-1-acetoxy-2-dimethylaminomethyl-cyclohexane melting at 150-155° C.

Example 2

Following the method described in example 1, using however 2.5 g of magnesium turnings, 18.7 g of m-bromoanisole dissolved in 80 ml of absolute tetrahydrofuran and 12.7 g of 2-dimethylaminomethyl-cycloheptanone dissolved in 25 ml of absolute tetrahydrofuran, one obtains in a yield of 73.8 % the 1-(m-methoxyphenyl)-2-dimethylaminomethyl-cycloheptanol-(1) boiling at 125° C/0.003 mm Hg. The hydrochloride melts at 177-181° C.

In the same manner there are obtained by reaction of m-methoxyphenyl-magnesiumbromide with the appropriate basic ketones the following compounds

a) 1-(m-methoxyphenyl)-2-morpholinomethyl-cyclohexanol-(1), boiling point 182-183° C/0.02 mm Hg, yield 43.7 %, melting point of the hydrochloride 231-233° C.

b) 1-(m-methoxyphenyl)-2-pyrrolidinomethyl-cyclohexanol-(1), boiling point 145-147° C/0.15 mm Hg, yield 55.5 %, melting point of the hydrochloride 174-178° C.

c) 1-(m-methoxyphenyl)-2-[N-methyl-N-(β-phenylethyl)-aminomethyl]- cyclohexanol-(1), boiling point 167° C/0.006 mm Hg, yield 56.7 % of theoretical.

Example 3

Five g of magnesium turnings are treated while stirring with a solution of 1 ml of ethylbromide in 15 ml of absolute tetrahydrofuran. To the warm reaction mixture is added a solution of 39.5 g of m-bromophenylbenxyl-ether in 150 ml of absolute tetrahydrofuran in such a rate that the mixture boils gently.

After being refluxed for one further hour, the mixture is chilled

to 0 to -10° C and at this temperature treated dropwise with a solution of 23.3 g of 2-dimethylaminomethyl-cyclohexanone in 45 ml of absolute tetrahydrofuran while stirring. The reaction mixture is stirred for 4 further hours at room temperature and then it is slowly poured to a stirred mixture of 25 g of ammonium chloride, 50 ml of water, and 50 g of ice. The layers are separated, the aqueous layer is extracted twice with 50 ml portions of ether. The combined organic layers are dried with sodium sulfate and evaporated. On distillation the residue yields the 1-(m-benzyloxyphenyl)-2-dimethylaminomethyl-cyclohexanol-(1), boiling at 156-160° C/0.003 mm Hg. Yield 61 % of theoretical. The hydrochloride of this compound melts at 141-143° C. By treating this hydrochloride with thionylchloride one obtains the hydrochloride of 1-(m-benzyloxyphenyl)-1-chloro-2-dimethylaminomethyl-cyclohexane melting after recrystallization from ethanol/ether at 150-151° C.

In the same manner there are obtained by reaction of m-benzyloxyphenyl-magnesiumbromide with the appropriate basic ketones the following compounds

a) 1-(m-benzyloxyphenyl)-2-dimethylaminomethyl-cycloheptanol-(1), boiling point 167-172° C/0.004 mm Hg, yield 45.3 %, melting point of the hydrochloride 140-143° C. Treatment with thionylchloride yields the hydrochloride of 1-(m-benzyloxyphenyl)-1-chloro-2-dimethylaminomethyl-cycloheptane, melting at 124-125° C.

b) 1-(m-benzyloxyphenyl)-2-pyrrolidinomethyl-cyclohexanol-(1), boiling point 175-178° C/0.0002 mm Hg, yield 27.4 %, melting point of the hydrochloride 171-173° C.

c) 1-(m-benzyloxyphenyl)-2-[N-methyl-N-(β-phenylethyl)-aminomethyl] -cyclohexanol-(1), boiling point 220-221° C/0.001 mm Hg, yield 46.6 %, melting point of the hydrochloride 173-175° C.

d) 1-(m-benzyloxyphenyl)-2-(N-methyl-N-benzylamino-methyl)-cyclohexanol-(1), boiling point 208-210° C/0.001 mm Hg, yield 40.1 %, melting point of the hydrochloride 188-190° C.

e) 1-(m-benzyloxyphenyl)-2-morpholinomethyl-cyclopentanol-(1), boiling point 200-205° C/0.007 mm Hg, yield 43.6 %, melting point of the hydro-

chloride 169-170° C.

Example 4

To 150 ml of absolute ether stored under an atmosphere of nitrogen are added 2.8 g of lithium in small pieces, and then, with stirring, a few ml of a solution of 27.5 g of butylbromide in 50 ml of absolute ether. When the reaction has started, the mixture is chilled to -10° C and the remaining portion of the solution of butylbromide is added dropwise.

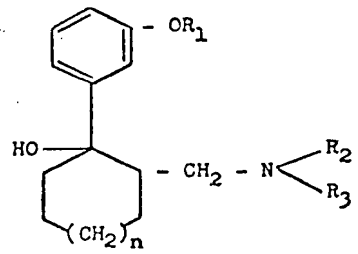
The reaction mixture is stirred for 2 hours at 0 to +10° C and then chilled to -40 to -50° C. A solution of 39.5 g of m-bromophenylbenzylether in a mixture of 60 ml of absolute ether and 90 ml of absolute tetrahydrofuran is then added slowly with stirring and then a solution of 23.3 g of 2-dimethylaminomethyl-cyclohexanone in 45 ml of absolute ether is added dropwise. Stirring of the reaction mixture is continued for 2 hours at -40° C. Then the reaction mixture is allowed to come slowly up to room temperature. The product is worked up in the same manner as described in examples 1 and 3. The same product as in example 3 is obtained in a yield of 49.1 %.

Example 5

The procedure is the same as in example 1. There are used, however, 5 g of magnesium turnings, 40.2 g of m-ethoxybromobenzene dissolved in 160 ml of absolute tetrahydrofuran and 23.3 g of 2-dimethylaminomethyl-cyclohexanone dissolved in 45 ml of absolute tetrahydrofuran. Thus there is obtained in a yield of 62.6 % 1-(m-ethoxyphenyl)-2-dimethylaminomethyl-cyclohexanol-(1), boiling at 134-135° C/0.02 mm Hg. Melting point of the hydrochloride 170-175° C.

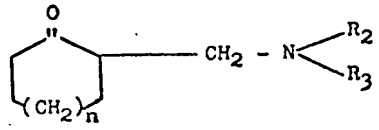
THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS :

1. The process for the preparation of analgesically active phenol ethers of the general formula I



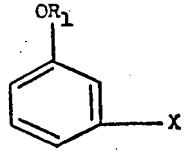
I

wherein R_1 represents an alkyl radical containing 1 to 3 carbon atoms or a phenyl alkyl radical having 1 to 3 carbon atoms in the alkyl group, R_2 and R_3 have the same or a different meaning and represent alkyl radicals containing 1 to 6 carbon atoms or phenyl alkyl radical having 1 to 3 carbon atoms in the alkyl group, or together with the nitrogen atom represent a morpholine or pyrrolidine group, and n represents zero, 1 or 2 and the pharmaceutically acceptable esters thereof with hydrogen halides or lower alkanoic acids, and the pharmaceutically acceptable acid addition salts of these compounds with acids, comprising reacting a compound of the general formula



II

wherein R_2, R_3 and n have the same meanings as given above with a compound of the general formula



III

wherein R_1 has the meaning given above and X represents a lithium atom or the group MgHal wherein Hal represents a halogen atom in the presence of an ether, hydrolyzing the compound thus obtained and when the ester is required esterifying the compounds of formula I thus obtained with lower alkanoic acids or

hydrogen halides and when the salt is required transforming the compounds obtained into salts with acids.

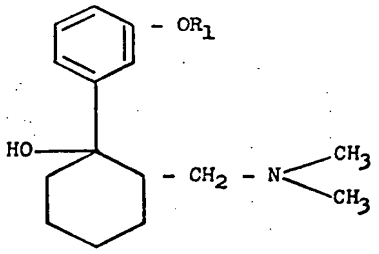
2. A process as claimed in claim 1 in which the ether is a cyclic ether.

3. A process as claimed in claim 1 in which the lower alkanoic acid is used in the form of an anhydride or halide thereof.

4. Phenol ethers of the general formula I given in claim 1, esters of these compounds with hydrogen halides or lower alkanoic acids or salts of these compounds with acids, whenever prepared by the processes claimed in claim 1, 2 or 3 or obvious chemical equivalents thereof.

5. A process as claimed in claim 1 in which in the reactants R_2 and R_3 are methyl and n is 1.

6. Phenol ethers of the general formula



I

wherein R_1 is an alkyl radical containing 1 to 3 carbon atoms or a phenyl alkyl radical having 1 to 3 carbon atoms in the alkyl group when prepared by the process of claim 5 or an obvious chemical equivalent thereof, or esters or salts thereof whenever prepared by the process as claimed in claim 5 or an obvious chemical equivalent thereof.

7. A process as claimed in claim 5 in which in the reactants R_1 is phenyl lower alkyl.

8. A phenol ether of general formula given in claim 6 or an ester or salt thereof when prepared by the process of claim 7 or an obvious chemical equivalent thereof.

9. A process as claimed in claim 1 in which 2-dimethylaminomethyl-cyclohexanone-(1) is reacted with m-methoxyphenyl-magnesium bromide in tetrahydrofuran.

10. 1-(m-methoxyphenyl)-2-dimethylaminomethyl-cyclohexanol-(1) or a salt or ester thereof, whenever prepared by the process as claimed in claim 9 or an obvious chemical equivalent thereof.

11. A process as claimed in claim 9 in which the product obtained is reacted with hydrogen chloride.

12. The hydrochloride of 1-(m-methoxyphenyl)-2-dimethylaminomethyl-cyclohexanol-(1), whenever prepared by the process as claimed in claim 11 or an obvious chemical equivalent thereof.

13. A process as claimed in claim 1 in which m-methoxyphenyl-magnesium-bromide is reacted with 2-dimethylaminomethyl-cycloheptanone in tetrahydrofuran.

14. 1-(m-methoxyphenyl)-2-dimethylaminomethyl-cycloheptanol, an ester or salt thereof when prepared by the process of claim 13 or an obvious chemical equivalent thereof.

15. A process as claimed in claim 1 in which m-methoxyphenyl-magnesium-bromide is reacted with 2-morpholinomethyl-cyclohexanone in tetrahydrofuran.

16. 1-(m-methoxyphenyl)-2-morpholinomethyl-cyclohexanol-(1) or a salt or ester thereof when prepared by the process of claim 15 or an obvious chemical equivalent thereof.

17. A process as claimed in claim 1 in which m-methoxyphenyl-magnesium-bromide is reacted with 2-pyrrolidinomethyl-cyclohexanone in tetrahydrofuran.

18. 1-(m-methoxyphenyl)-2-pyrrolidinomethyl-cyclohexanol-(1) or salt or ester thereof when prepared by the process of claim 17 or an obvious chemical equivalent thereof.

19. A process as claimed in claim 1 in which m-methoxyphenyl-magnesium-bromide is reacted with 2-[N-methyl-N-(β-phenylethyl)aminomethyl]-cyclohexanone in tetrahydrofuran.

20. 1-(m-methoxyphenyl)-2-[N-methyl-N-(β-phenylethyl)aminomethyl]-cyclohexanol-(1) when prepared by the process of claim 19 or an obvious chemical equivalent thereof.

21. A process as claimed in claim 1 in which m-benzyloxyphenyl-magnesiumbromide is reacted with 2-dimethylaminoethyl-cyclohexanone in tetrahydrofuran.

22. 1-(m-benzyloxyphenyl)-2-dimethylaminomethyl-cyclohexanol-(1) or an ester or salt thereof when prepared by the process of claim 21 or an obvious chemical equivalent thereof.

23. A process as claimed in claim 1 in which m-benzyloxyphenyl-magnesiumbromide is reacted with 2-dimethylaminomethyl-cycloheptanone in tetrahydrofuran.

24. 1-(m-benzyloxyphenyl)-2-dimethylaminomethyl-cycloheptanol-(1) or salt or ester thereof when prepared by the process of claim 23 or an obvious chemical equivalent thereof.

25. A process as claimed in claim 1 in which m-benzyloxyphenyl-magnesiumbromide is reacted with 2-pyrrolidinomethyl-cyclohexanone in tetrahydrofuran.

26. 1-(m-benzyloxyphenyl)-2-pyrrolidinomethyl-cyclohexanol-(1) or a salt or ester thereof when prepared by the process of claim 25 or an obvious chemical equivalent thereof.

27. A process as claimed in claim 1 in which m-benzyloxyphenyl-magnesiumbromide is reacted with 2-[N-methyl-N-(β-phenylethyl)aminoethyl]-cyclohexanone in tetrahydrofuran.

28. 1-(m-benzyloxyphenyl)-2-[N-methyl-N-(β-phenylethyl)aminoethyl]-

cyclohexanol-(1) or salt or ester thereof when prepared by the process of claim 27 or an obvious chemical equivalent thereof.

29. A process as claimed in claim 1 in which m-benzyloxyphenyl-magnesiumbromide is reacted with 2-morpholino-cyclopentanone in tetrahydrofuran.

30. 1-(m-benzyloxyphenyl)-2-morpholino-cyclopentanol-(1) or salt or ester thereof when prepared by the process of claim 29 or an obvious chemical equivalent thereof.

31. A process as claimed in claim 1 in which m-ethoxyphenyl-magnesiumbromide is reacted with 2-dimethylaminomethyl-cyclohexanone in tetrahydrofuran.

32. 1-(m-ethoxyphenyl)-2-dimethylaminomethyl-cyclohexanol-(1) or a salt or ester thereof when prepared by the process of claim 31 or an obvious chemical equivalent thereof.

33. A process as claimed in claim 1 in which the product obtained is associated with a pharmaceutically acceptable carrier.

34. A composition comprising a compound of formula I given in claim 1 or a salt or ester thereof and a pharmaceutically acceptable carrier when prepared by the process of claim 33 or an obvious chemical equivalent thereof.